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TITLE: Developing Gene Silencing for the Study and Treatment of Dystonia

PRINCIPAL INVESTIGATOR: Pedro Gonzalez-Alegre, MD, PhD

CONTRACTING ORGANIZATION: The Children's Hospital of Philadelphia
Philadelphia, PA 19104

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Pedro Gonzalez-Alegre

Email: gonzalezap@email.chop.edu

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The Children's Hospital of Philadelphia
Research Institute
3501 Civic Center Blvd
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14. ABSTRACT

Dystonia is a disabling and incurable neurological disorder characterized by twisting movements that cause significant disability. Some forms of dystonia are caused by genetic mutations and, therefore, passed on from generation to generation. The most common form of early onset genetic dystonia is a disease known as DYT1, in which children around age ten develop dystonia, usually in a leg or arm, and over 2 or 3 years spreads to affect all body parts causing substantial disability. There is no cure for DYT1. Therefore, the development of new treatments for DYT1 is a priority in dystonia research.

Here, based on prior scientific reports from our research group and other investigators, we hypothesize that we could use two complementary approaches, known as RNA interference or antisense oligonucleotide therapy, to prevent neurons from making the mutated or "toxic" protein that causes DYT1 dystonia. By doing this in the appropriate brain region, we should be able to reverse the symptoms of the disease. We have already demonstrated that this is possible but using cells growing in a dish in the laboratory, not in living animals. In this project, we aim to answer several specific questions: *Is this treatment approach helpful and safe? What is the area of the brain in which we should inject this RNA interference vector to eliminate the symptoms? Are the motor deficits in DYT1 dystonia reversible?* We propose to use a novel rat model of DYT1 dystonia and infuse antisense oligonucleotides or viral vectors mediating RNA interference to suppress expression of the mutated protein in their brain. They will target different areas of the brain, and we will measure if they are able to reverse known abnormalities that occur in the brain of DYT1 rats, including abnormal motor function. More importantly, we will check if no side effects or toxicity occurs. Successful completion of our studies will move us a step closer to design of what is known as a phase 1 safety trial in humans afflicted by this debilitating disease. This would be a giant milestone in dystonia research. In addition, these studies will provide very helpful information on the areas of the brain that are responsible, not only for DYT1, but also for other forms of dystonia

15. SUBJECT TERMS

Nothing listed

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1. INTRODUCTION

Dystonia is a debilitating neurological disease with no cure that is characterized by involuntary muscle contractions that cause abnormal twisting postures. DYT1 dystonia, an autosomal dominant disease, the most common early onset inherited dystonia. DYT1 is caused by a common deletion of a single amino acid (ΔE) in torsinA. Abundant evidence suggests that suppressing expression of torsinA(ΔE) through gene silencing would be beneficial. Our overall hypothesis is suppressing expression of torsinA(ΔE) through RNA interference (RNAi) or antisense oligos (ASO) will be a safe an effective treatment for DYT1 dystonia. In innovative proposal, we use a rat model of DYT1 to test the efficacy and safety of viral (AAV)-mediated RNAi or intraventricular delivery of ASO in vivo. Key questions on dystonia research that we will address are whether the DYT1 phenotype is reversible and what is the neuroanatomical substrate that causes motor dysfunction in dystonia.

2. KEYWORDS

adeno-associated virus (AAV); antisense oligonucleotide (ASO); RNA interference (RNAi); torsinA; DYT1; dystonia; gene silencing; cerebellum; striatum; therapy;

3. ACCOMPLISHMENTS

We will briefly summarize the accomplishments from months 1-12 (previous reporting period, submitted in August 2015), to then list the major goals of the project as stated in the approved SOW for months 13-24 (this reporting period) and describe the status of those goals.

Summary of accomplishments in previous reported period (Year 1, Months 1-12, described in more detail in progress report submitted in August 2015)

The bulk of the experiments planned for year 1 (task 2) consisted on infusing different doses of the ASOs into the lateral ventricle of 2-month-old DYT1 and control rats to identify efficacy and toxicity thresholds. Behavioral evaluation was completed at baseline. Subsequently, an osmotic pump with ASO (active or missense control) was

inserted in the mid-scapular subcutaneous space and its tip placed into the lateral ventricle. We used 3 different doses (50, 100 or 200 µg/day). The infusion lasted for 14 days. The rats underwent repeated behavioral testing after the infusion and were sacrificed. Their brains were extracted for mRNA, protein and histological analyses. To determine silencing efficacy, we planned to measure levels of torsinA mRNA and protein with RTPCR and western blotting. By Month 12, all animals for the 100 and 200 µg/day completed the protocol, were sacrificed and protein, mRNA and fixed brain collected for analysis. Half of the animals of the 50 µg/day group also completed the protocol. The remainder 50% were set to receive the infusion and complete the protocol in Year 2.

What were the major goals of the project?

Light grey font indicates experimental plan form months 1-12 (previous reporting period), black font experimental plan for months 13-24 (current reporting period) and blue font for months 25-36 (next reporting period)

Task 1. Regulatory review and approval processes for animal studies (2-4 months).

Task 2. Dose-finding experiments with ASO in DYT1 knock in rats. There are two genotypes (DYT1 and WT), two different ASO (#3 and MIS) and three doses of each. Therefore, there are a total of 12 experimental groups, each comprised of 12 rats. This experiment will require 72 DYT1 KI rats and 72 wild type littermates. DYT1 rats reproduce with mendelian frequency. We will need to generate 144 total mice (72 WT and 72 DYT1). We will complete this study with four separate cohorts (4 weeks apart) due to the required number of animals. Once tissues are collected, they will be processed simultaneously (both histology and molecular studies).

2a. Animal cohort 1:

1) Generation of animal cohort 1 (months 1-4). We will generate 2 month-old rats (18 DYT1 and 18 WT).
2) Baseline behavior (month 4)
3) Infusion of ASO during 2 weeks (month 4-5)
4) Post-infusion behavioral testing/sacrifice (month 5)
5) Molecular and histological analyses (months 8-14)

2b. Animal cohort 2:

1) Generation of animal cohort 2 (months 2-5). We will generate 2 month-old rats (18 DYT1 and 18 WT).
2) Baseline behavior (month 5)
3) Infusion of ASO during 2 weeks (month 5-6)
4) Post-infusion behavioral testing/sacrifice (month 6)
5) Molecular and histological analyses (months 8-14)

2c. Animal cohort 3:

1) Generation of animal cohort 3 (months 3-6). We will generate 2 month-old rats (18 DYT1 and 18 WT).

2) Baseline behavior (month 6)
3) Infusion of ASO during 2 weeks (month 6-7)
4) Post-infusion behavioral testing/sacrifice (month 7)
5) Molecular and histological analyses (months 8-14)

2d. Animal cohort 4:

1) Generation of animal cohort 4 (months 4-7). We will generate 2 month-old rats (18 DYT1 and 18 WT).
2) Baseline behavior (month 7)
3) Infusion of ASO during 2 weeks (month 7-8)
4) Post-infusion behavioral testing/sacrifice (month 8)
5) Molecular and histological analyses (months 8-14)

Task 3. Therapeutic trial with ASO in DYT1 rats. Once a dose has been selected from previous studies, a therapeutic study will be conducted in DYT1 transgenic males and control littermates. As the primary outcome of this experiment is behavior, we will use only males. This experiment includes two genotypes (DYT1 and WT) and two ASO (#3 and MIS) at a single dose. Each experimental group includes 16 animals. Therefore, this experiment will require 32 DYT1 KI and 32 wild type littermates. DYT1 mice reproduce with mendelian frequency. Expecting a 50:50 male:female ratio, we will need to generate 128 total rats (64 WT and 64 DYT1). Because these animals will be used once they reach 12 months of age, and due to the inherent variability in genotypes and sex of animals obtained, we expect to generate a cohort of ~175 rats. Females will be sacrificed early and males of both genotypes will be maintained to reach the experimental age. We will complete this study with two separate cohorts (4 weeks apart) due to the required number of animals.

3a. Animal cohort 1:

1) Generation of animal cohort 1 (months 6-18). We will generate 12 month-old male rats (16 DYT1 and 16 WT).
2) Baseline behavior (months 18)
3) Infusion of ASO during 4 weeks (months 19)
4) Post-infusion behavioral testing all animals (months 19-20).
5) Sacrifice of half of animals in each group (month 19-20)
6) Behavioral testing in all surviving animals (months 21-22).
7) Sacrifice of all surviving animals (month 21-22)
8) Molecular and histological analyses (months 22-28)

3b. Animal cohort 2:

1) Generation of animal cohort 2 (months 7-19). We will generate 12 month-old male rats (16 DYT1 and 16 WT).
2) Baseline behavior (months 19)
3) Infusion of ASO during 4 weeks (months 20)
4) Post-infusion behavioral testing all animals (months 20-21).
5) Sacrifice of half of animals in each group (month 20-21)
6) Behavioral testing in all surviving animals (months 22-23).
7) Sacrifice of all surviving animals (month 22-23)

8) Molecular and histological analyses (months 23-28)

Task 4. To generate AAV2/1.CMVGFP.miRNA. We have shuttle plasmids to generate these viruses. We anticipate requiring only one prep from each virus (active and control) for the proposed experiments. We will give the shuttle plasmids to the Vector Core Facility in month 6, and expect to receive the viruses in month 7. We will do a pilot study in cultured HEK cells monitoring for GFP expression by fluorescence microscopy to verify expression (month 7).

Task 5. To evaluate the efficacy and safety of AAV-RNAi in striatum and cerebellum of DYT1 rats. As the primary outcome of this experiment is behavior, we will use only males. This experiment includes two genotypes (DYT1 and WT), two AAV (miTorA and miMIS) and two target tissues (cerebellum and striatum) at a single dose. Each experimental group (8 total) includes 12 animals. Therefore, this experiment will require 48 DYT1 KI and 48 wild type littermates. DYT1 mice reproduce with mendelian frequency. Expecting a 50:50 male:female ratio, we will need to generate 192 total rats (96 WT and 96 DYT1). Because these animals will be used once they reach 12 months of age, and due to the inherent variability in genotypes and sex of animals obtained, we expect to generate a cohort of ~250 rats. Females will be sacrificed early and males of both genotypes will be maintained to reach the experimental age. We will complete this study with two separate cohorts (4 weeks apart) due to the required number of animals.

4a. Animal cohort 1 (targeting striatum):

1) Generation of animal cohort 1 (months 12-24). We will generate 12 month-old male rats (24 DYT1 and 24 WT).
2) Baseline behavior (months 24)
3) Injection of AAV into striatum (month 25)
4) Post-injection behavioral testing#1 (month 26).
5) Post-injection behavioral testing#2/sacrifice (months 28-29)
6) Molecular and histological analyses (months 30-36)

4b. Animal cohort 1 (targeting cerebellum):

1) Generation of animal cohort 2 (months 13-25). We will generate 12 month-old male rats (24 DYT1 and 24 WT).
2) Baseline behavior (months 25)
3) Injection of AAV into cerebellum (month 26)
4) Post-injection behavioral testing#1 (month 27).
5) Post-injection behavioral testing#2/sacrifice (months 29-30)
6) Molecular and histological analyses (months 30-36)

Deviations from Initial Plan:

As described below, completion of tasks 1 and 2 led us to conclude that ASO#3 does not reduce expression of torsinA(ΔE) transgenic in rats *in vivo*. Furthermore, there is a suggestion of toxicity that might be enhanced in transgenic rats over wild type littermates. As a consequence, it did not make sense to complete the proposed Task 3.

Task #3 was proposed as a therapeutic trial of ASO#3 in aged rats using the dose identified as efficacious in Task#2. As we found no efficacy with any dose, and in fact detected potential toxicity (as potentially predicted in the Alternative Outcomes and Strategies section of the initial application), we decided to move on a few months earlier than predicted to initiate Tasks #4 and #5. Therefore, at Month 23 we are performing experimental steps proposed for Month 26.

What was accomplished of the goals for Year 2, Months 13-24?

A) Completion of Task#2:

Task#2 was initiated in Year 1. As justified in the Progress Report for the previous reporting period, experiments were delayed 1-2 months in the initial year. Thus, instead of being completed at Month 14, at the beginning of the current reporting period the plan was to complete them in Month 16. Due to the unexpected results (lack of silencing), outcome measures had to be replicated several times to eliminate the possibility of technical problems (technical replicates, no biological replicates).

At the end of Year 1 (Month 12), all animals for the 100 and 200 µg/day completed the protocol, were sacrificed and protein, mRNA and fixed brain collected for analysis. Half of the animals of the 50 µg/day group also completed the protocol. The remainder 50% were set to receive the infusion and complete the protocol in Year 2.

In Year #2, we completed all the injections in the 50% of animals pending from the µg/day group. Subsequently, these animals were sacrificed as planned and their brains extracted for analysis (mRNA, protein and immunohistology).

From all experimental animals from Task #2, in Months 14-20 we completed extensive analysis, including technical replicates to verify the validity of the findings. This included expression levels of torsinA by RTPCR and western blotting from multiple brain regions, behavioral analysis at baseline (in Year 1) and after the infusion (Years 1 and 2), and evaluation for histological markers of torsinA expression, glial reaction and neuronal loss.

These analyses disclosed the following information:

- Behavioral analyses: as reported, baseline analysis showed abnormal clasping and gait in DYT1 transgenic rats when compared to controls, but no differences on performance on the rotarod and open field (figure 1 and not shown). After the injections, the following was observed: there was no statistically significant effect of any of the treatment groups. However, there as a trend towards a dose-dependent worsening of the clasping phenotype in the groups that received either ASO (Missense or ASO#3), more obvious for DYT1 transgenic rats than controls (figure 2 and not shown). This suggested the possibility of toxicity by the ASOs, and possible increased susceptibility for this toxic effect in DYT1 rats.

- Protein analysis of different brain regions by western blotting showed no evidence of silencing by ASO#3 when compared to control missense or vehicle (figure 3 and not shown).

- mRNA analysis of different brain regions by QPCR showed no evidence of silencing by ASO#3 when compared to controls missense or vehicle (figure 4 and not shown).

- Neurohistological analysis of efficacy: blinded quantification of optical density did not show significant changes in torsinA immunostaining. However, we found a trend toward increased astroglial reaction (increase staining by the marker of activated astrocytes GFAP) in both ASOs (missense and #3) (figure 5 and not shown). Furthermore, this seemed to be more pronounced in DYT1 transgenics rats than controls, suggesting this might not be a valid therapeutic option for DYT1.

Upon the conclusion of Tasks #1 and #2 in Years 1 and 2, we could conclude that ASO#3 is not a viable therapeutic option for DYT1. As a result, we decided to not complete Task #3 (therapeutic trial of ASO#3 in aged rats) and proceed to Tasks #4-5.

B) Completion of Task #4.

Using previously designed shuttle plasmids, we generated AAV1 encoding microRNAs targeting human torsinA(ΔE) and a missense sequence. Because we will not complete Task#3, we decided to generate two different microRNAs targeting human torsinA(ΔE) and two missense controls viruses, instead of one of each as initially proposed. By having two different sequences we will verify that any biological effects observed are not related to sequence specific off-target effects. We generated one prep for each virus (2 active and 2 controls) in the Vector Core Facility. We have completed a pilot study in cultured HEK cells monitoring for GFP expression by fluorescence microscopy and measuring levels of co-transfected human torsinA(ΔE) to verify expression and silencing (figure 6). Thus, Task#4 has been successfully completed.

C) Initiation of Task#5.

- Animals cohorts 1 and 2 have been generated.

- Baseline behavioral evaluation has been completed (not analyzed yet as the evaluators will be blinded to genotype until completion of the experiment).

- Eight animals received pilot injections into striatum and cerebellum to verify infectivity of the AAV1. These animals have been sacrificed and their brains are undergoing analysis for GFP expression and torsinA silencing.

- Intrastriatal injections have been performed in 10 animals as of August 15th.

Elimination of Task#3 led us to perform in Month 24 experiments planned for Month 26. This has allowed us to add 2 additional viral constructs (a second active microRNA and

a second control microRNA). Thus, we are still aiming to complete the project on time and within the proposed budget.

Figures

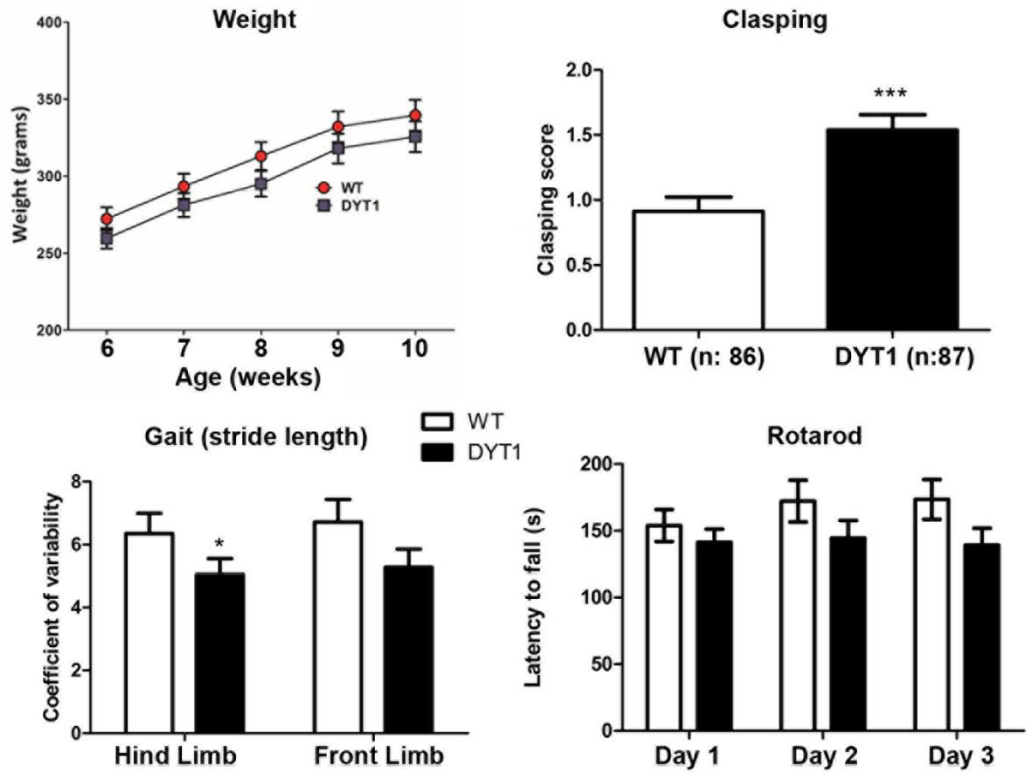

Figure 1. Baseline behavioral analysis. DYT1 transgenic (n: 87) and control WT littermates (n: 86) underwent behavioral evaluation at 3-4 weeks of age before implantation of an Alzet pump to receive ASO or control injections

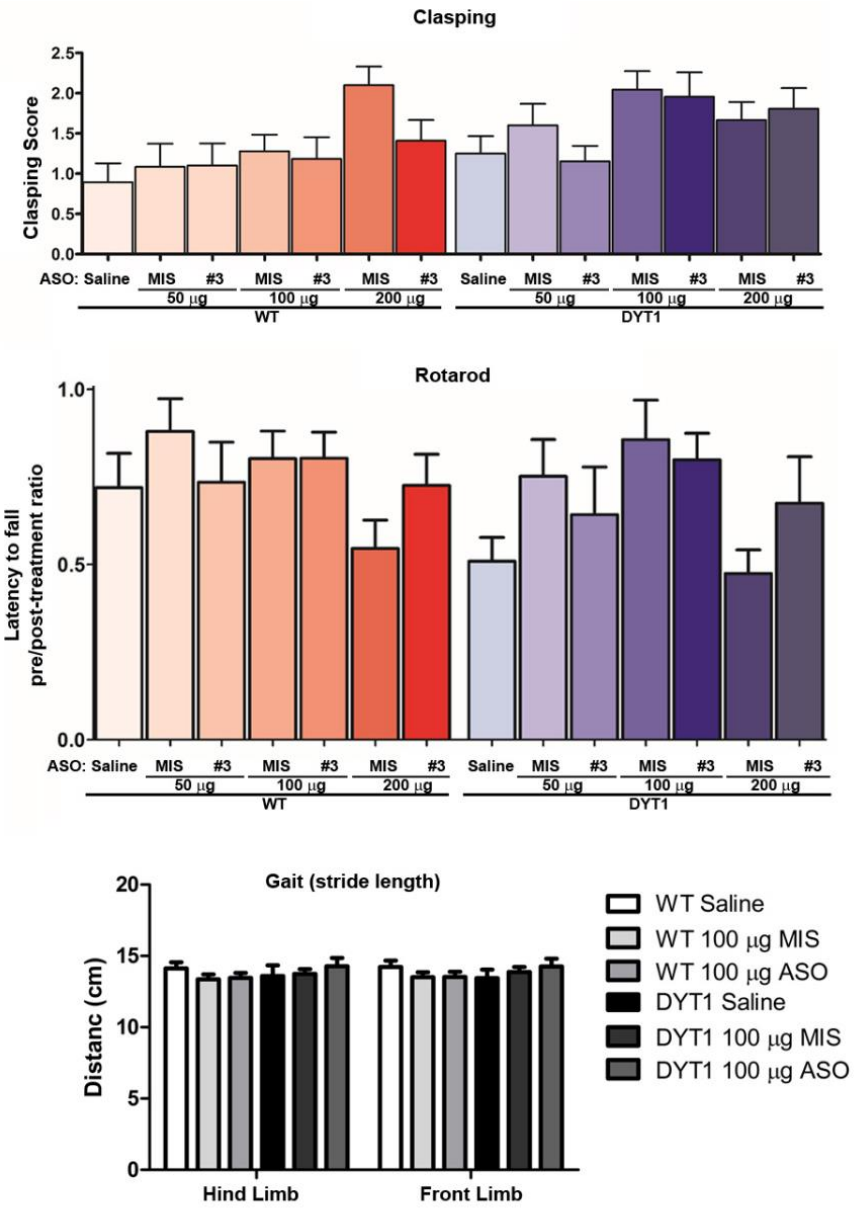

Figure 2. Post-infusion behavioral analysis. DYT1 transgenic and control WT littermates received either saline or increasing concentrations of ASO#3 (active) or a missense ASO (control) and underwent behavioral evaluation during the 2 weeks after the infusion was completed. There was a trend towards worse clasping scores in DYT1 transgenic animals receiving any ASO (active or control) over those receiving saline.

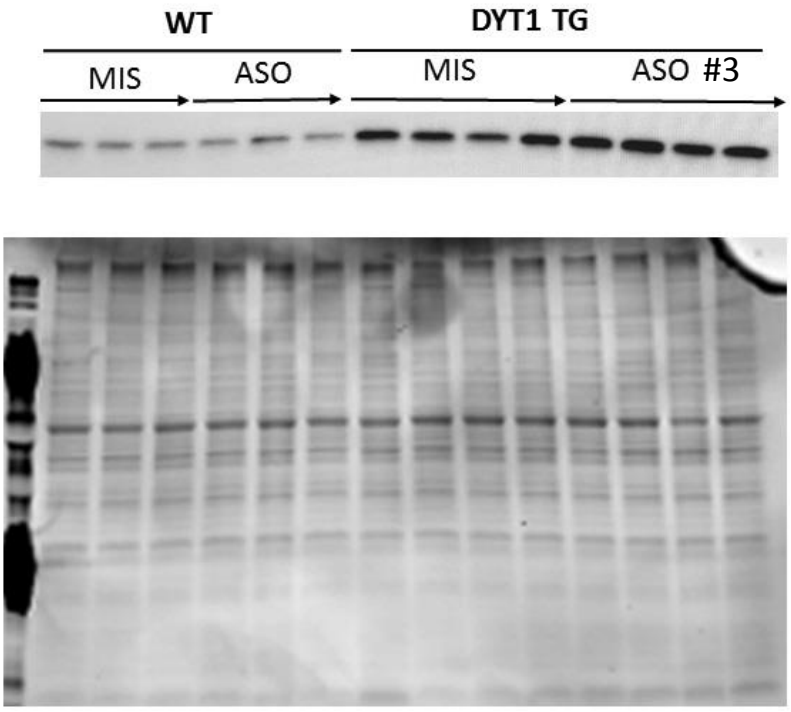

Figure 3. Western blot analysis of htorsinA(ΔE) expression showed increased torsinA expression in DYT1 transgenic rats over WT as expected. However, it did not show any evidence of silencing by the active ASO#3 over control missense. Shown is a representative blot of prefrontal cortex tissue. Similar results were obtained in other tissues such as striatum and cerebellum.

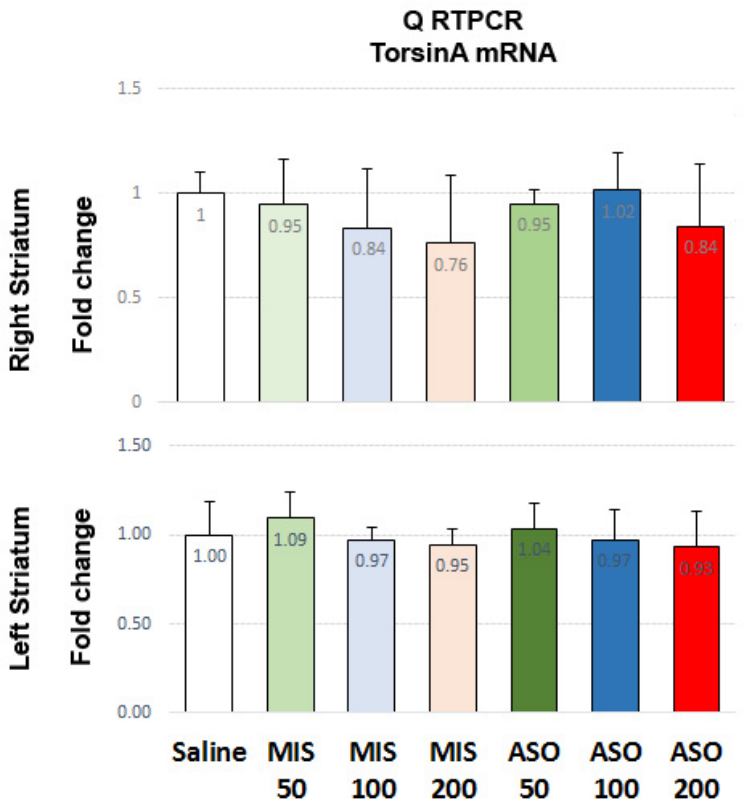

Figure 4. Q-RT-PCR analysis of htorsinA(ΔE) expression in DYT1 transgenic rats (the human transgene was not detected in WT controls). There was no evidence of silencing by the active ASO over control missense). Shown is a representative blot of striatal tissue. Similar results were obtained in other tissues such as prefrontal cortex and cerebellum.

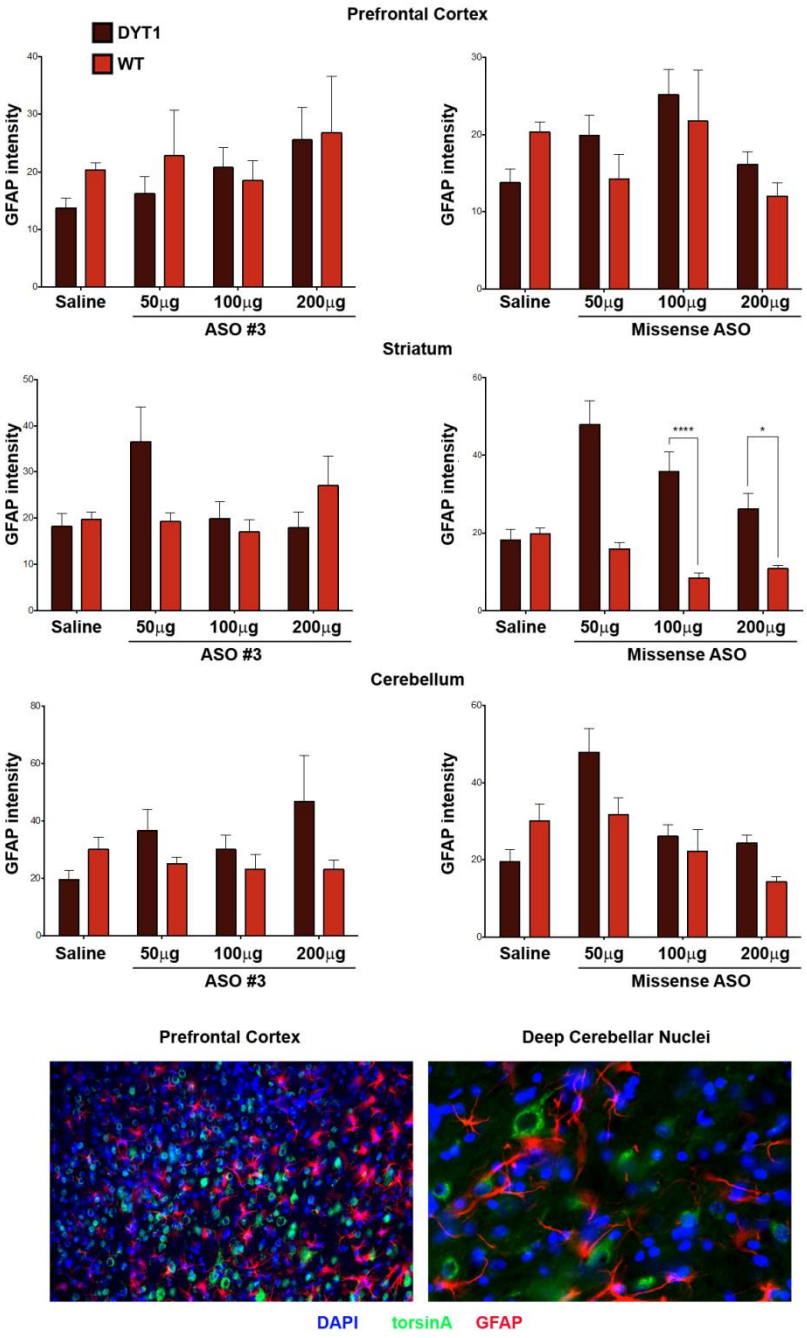

Figure 5. Immunofluorescence microscopy analysis of activated GFAP (marker of astroglial reaction) in different brain regions (quantified 3 equivalent slides per animal from each region selected). We found a trend and at times a significant increase in GFAP optical density (systematically measured by a blinded reader) caused by either ASO (active or control) and more pronounced in DYT1 transgenic rats, indicating a susceptibility towards toxicity driven by this genotype. Below are shown representative images (20X in cortex and a digitally magnified detail of deep cerebellar nuclei) demostrating the quality of the statining for torsinA and GFAP). We found no differences in torsinA expression in any brain region (quantification not shown)

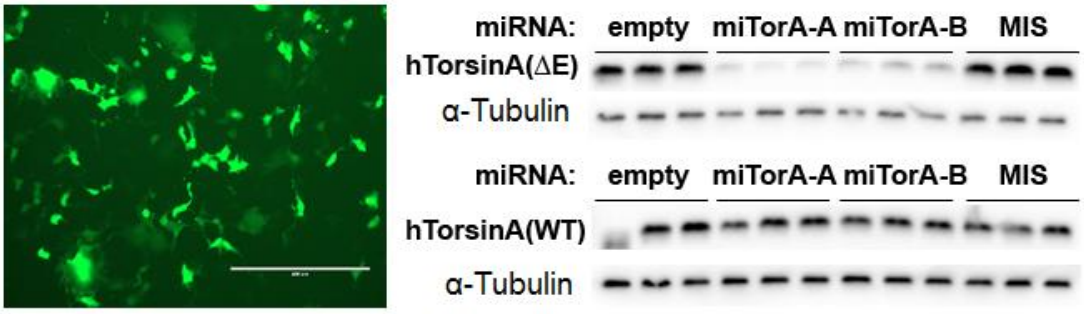

Figure 6. Generation of AAV1 expressing miRNAs targeting human torsinA(ΔE). AAV1 were generating expressing only GFP as a reporter of transduction (empty), or GFP and miRNAs targeting human torsinA(ΔE) (miTorA-A and miTorA-B) or a missense miRNA (MIS). HEK293 cells were cotrasnfected with these constructs and either human torsinA(ΔE) or human torsinA(WT). Immunofluorecence analysis demonstrated efficient cell transfection. Western blot analysis demonstrated efficient silencing of human torsinA(ΔE) by the two miRNA targeting this transcript, but no silencing of the human torsinA(WT) cDNA (demonstrating allele-specificity)

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

The main bulk of the next reporting period (months 24-36) will be to complete Task #5. The animal cohorts needed have been generated and are aging, baseline behavioral evaluations have been completed and injections have started. The goal of those experiments is to determine if suppressing expression of mutant torsinA in striatum or cerebellum using AAV1 reverses the motor phenotype in aged DYT1 rats.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

The lack of silencing of ASO#3 *in vivo* suggests that this sequence is not therapeutically helpful for DYT1 dystonia. Furthermore, the presence of potential heightened toxicity in transgenic rats suggest that perhaps this mutation makes the mammalian brain more

susceptible to ASO-toxicity and this is not a reasonable therapeutic approach for this disease.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS.

Changes in approach and reasons for change

As described below, completion of tasks 1 and 2 led us to conclude that ASO#3 does not reduce expression of torsinA(ΔE) transgenic in rats *in vivo*. Furthermore, there is a suggestion of toxicity that might be enhanced in transgenic rats over wild type littermates. As a consequence, it did not make sense to complete the proposed Task 3. Task #3 was proposed as a therapeutic trial of ASO#3 in aged rats using the dose identified as efficacious in Task#2. As we found no efficacy with any dose, and in fact detected potential toxicity (as potentially predicted in the Alternative Outcomes and Strategies section of the initial application), we decided to move on a few months earlier than predicted to initiate Tasks #4 and #5. Therefore, at Month 23 we are performing experimental steps proposed for Month 26.

Actual or anticipated problems or delays and actions or plans to resolve them.

The consequence of eliminating Task#3 on the timeline is that we are 2 months ahead despite starting Year-2 two months behind schedule. This has allowed us to add 2 additional viral constructs (a second active microRNA and a second control microRNA). Consequently, we are still aiming to complete the project on time and within the proposed budget.

Changes that had a significant impact on expenditures.

None (see above).

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents.

None

6. PRODUCTS.

Publications, conference papers, and presentations.

None.

Website(s) or other Internet site(s)

None.

Technologies or techniques

None.

Other Products

None.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS.

What individuals have worked on the project?

Name: Pedro Gonzalez-Alegre
Project Role: PI
Nearest person month worked: 3
Contribution to Project: No change.

Name: Beverly Davidson
Project Role: Co-Investigator
Nearest person month worked: 1
Contribution to Project: No change.

Name: Genevieve Beauvais
Project Role: Postdoctoral Associate
Nearest person month worked: 12
Contribution to Project: No change.

Name: Jaime Watson
Project Role: Research Technician II
Nearest person month worked: 12
Contribution to Project: Ms. Watson assists Dr. Beauvais in colony maintenance, animal genotyping, surgeries, behavioral, histological and molecular assessments.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Gonzalez-Alegre has the following changes to report:

New Grants

UH2N5094355; Davidson (PI) 1/1/16-12/30/16 1.8 cal mos
RNAi Therapy for Spinocerebellar Ataxia Type 1

Collaborative Center for X-Linked Dystonia Parkinsonism (CCXDP); Gadue (PI)
3/1/16-2/28/17 0.6 cal mos
Response of DYT3 iPSC to ER and Metabolic Stressors

Penn Institute on Aging Pilot Grant; Gonzalez-Alegre (PI) 7/1/16-6/30/17 .24 cal mos
Exploring functional and structural neuroimaging biomarkers of Huntington's disease progression

Terminated: None

Dr. Davidson has the following changes to report:

New Grants

PICALM Gene Therapy Zlokovic (PI) 10/1/15-9/30/16 .48 cal months
Cure Alzheimer's Fund

UH2N5094355; Davidson (PI) 1/1/16-12/30/16 1.8 cal mos
RNAi Therapy for Spinocerebellar Ataxia Type 1

Intellia Therapeutics, Inc.; Davidson (PI) 1/1/16-12/31/17 1.2 cal mos
Lipid Nanoparticle (LNP) Delivery of Cas9/gRNA to the CNS

Terminated

R56NS093392; Hughes (PI) 7/1/15-6/03/16 1.2 months
Mechanisms of RRAS Regulation of Huntington Toxicity & Turnover

R56NS090390; Thompson (PI) 9/30/14-8/31/15 .96 cal months
Neuroregulatoy Mechanisms of PIAS1 and Implications for Huntington's Disease

R21 NS077516; Davidson (PI) 07/01/12-06/30/16 .24 cal/months
Advancing gene therapy for late infantile neuronal ceroid lipofuscinosis

R21 NS084475; Davidson (PI) 07/01/13-06/30/16 .24 cal/months
Next Generation Gene Silencing strategies for Huntington's Disease

R21 NS084424; Davidson (PI) 09/01/13-8/31/16 .24 cal/months
Investigating cell-type-specific contribution to JNCL

P01HL64190; Poncz (PI) 7/1/14-6/30/16 .6 cal/months

Gene Therapy for Hemophilia

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS.

None

9. APPENDICES.

None.